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α-Diazo β-Keto Ester as Precursor to Aromatic C–H Insertion and Wolff Rearrangement with Different Directing Groups

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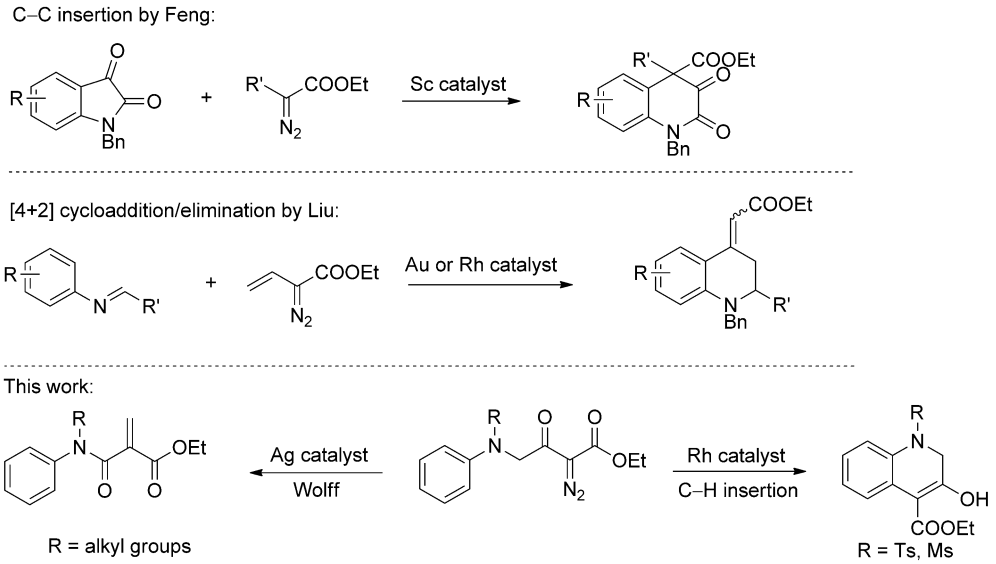
Abstract: A tunable aromatic C–H insertion and a Wolff rearrangement of α-diazo β-keto esters precursor were developed. Different directing groups on nitrogen led with high selectivity to either dihydroquinoline or 2-carbamoylacrylate motifs, which can be transformed to multiple heterocyclic scaffolds.

Keywords: C–H insertion; diazo compounds; heterocycles; rearrangement; synthetic methods

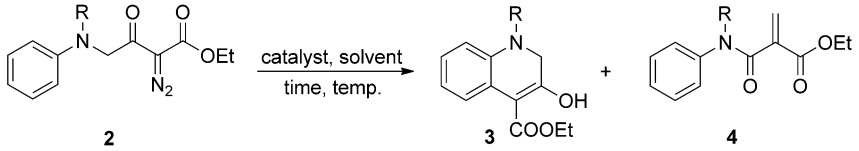
The aromatic C–H insertion and rearrangement of diazo compounds represent simple and powerful approaches for the construction of structurally unique frameworks.[1–3] The robust methods have been extensively explored in the transition metal-catalyzed C–H activation, allowing access to a number of nitrogen-containing heterocycles, such as dihydropyridones, β-lactams, pyridines, isoindolones, and bridged polycyclic rings.[4] Due to their prevalence in natural products and medicinal molecules, increasing the ability to access nitrogen-containing heterocycles is very important in the medicinal research.

Quinoline and quinolone, as valuable scaffolds, are the core structures of many bioactive molecules, including quinine,[5a] primaquine,[5b] cinchocaine,[5c] camptothecin,[5d] and brequinar.[5e] For example, Feng reported recently that an intermolecular C–C insertion of a α-diazo ester to isatin produced asymmetrical oxoquinolines. The key step in their transformations is a 1,2-aryl migration catalyzed by the scandium *N*,*N*′-dioxide complex (Scheme 1, *top*).[6] Concurrent work by Liu took advantage of the Povarov cycloaddition and carbene elimination as well to generate the tetrahydroquinoline ring regioselectively by treatment



Scheme 1. Construction of quinoline ring with carbenoids.

Table 1. Condition screening.[a]



2 3 4

Entry	**2** (R)	Catalyst	Solvent	Temp. [°C]/Time [h]	Yield [%][b]	
					3	**4**
1	**2a** (Ts)	$Rh_2(OAc)_4$	CH_2Cl_2	25/6	7	0
2	**2a** (Ts)	$Rh_2(esp)_2$	CH_2Cl_2	25/6	75	0
3	**2a** (Ts)	$Rh_2(esp)_2$	DCE	25/6	68	0
4	**2a** (Ts)	$Rh_2(esp)_2$	toluene	25/6	22	0
5	**2a** (Ts)	$Rh_2(esp)_2$	dioxane	25/6	34	0
6	**2a** (Ts)	AgOTf	CH_2Cl_2	25/6	ND[c]	
7	**2a** (Ts)	$Cu(acac)_2$	CH_2Cl_2	25/6	NR[d]	
8	**2b** (Ms)	$Rh_2(esp)_2$	CH_2Cl_2	25/6	61	0
9	**2c** (Ac)	$Rh_2(esp)_2$[e]	CH_2Cl_2	25/6	<5	0
10	**2d** (Me)	$Rh_2(esp)_2$	CH_2Cl_2	25/3	0	84
11	**2d** (Me)	$Rh_2(OAc)_4$	CH_2Cl_2	25/3	0	73
12	**2d** (Me)	CuI	CH_2Cl_2	40/6	ND[c]	
13	**2d** (Me)	CuOTf	CH_2Cl_2	40/6	0	<5
14	**2d** (Me)	Ag_2O	CH_2Cl_2	40/6	0	31
15	**2d** (Me)	Ag_2O	toluene	100/3	0	92
16	**2d** (Me)	$Rh_2(OAc)_4$	toluene	100/3	0	66
17	**2d** (Me)	Ag_2O	dioxane	100/3	0	68
18	**2d** (Me)	Ag_2O	DCE	80/3	0	71
19	**2d** (Me)	none[f]	toluene	100/6	0	21

[a] *Reaction conditions:* **2** (0.2 mmol) and catalyst (0.5 mol%) in solvent (2 mL).
[b] Yields are given for isolated products after silica gel purification.
[c] Not determined (ND), a mixture of complex products.
[d] No reaction (NR).
[e] Catalyst loading (1.0 mol%).
[f] Without catalyst.

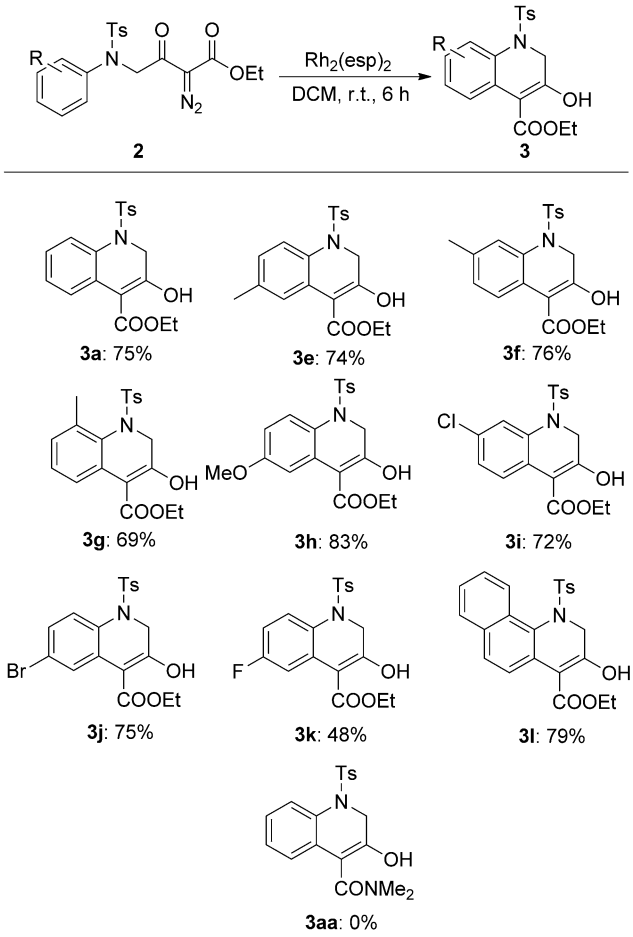
with different gold and rhodium catalysts (Scheme 1, *middle*).[7] However, elegant examples to construct quinoline heterocycles using diazo precursors are still challenging compared to the thermaldynamically favoured benzo five-membered counterparts.[8] In the view of the importance of diverse α-diazo carbonyl compounds and for expanding the synthetic utility to quinoline structures, we employed diazo precursors in the intramolecular aromatic C–H insertion to provide functionalized quinoline rings. In the meantime, we found that the α-diazo β-keto ester precursors bearing different directing groups on nitrogen can also undergo an unprecedent Wolff rearrangement (Scheme 1, *bottom*).[9] Here, we wish to describe the development of this tunable aromatic C–H insertion and rearrangement reaction to access multiple heterocyclic building blocks, which show a novel divergent-oriented synthetic pattern in the chemistry of diazo compounds.[10]

We began our investigations from the synthesis of α-diazo β-keto esters **2** with different directing groups on the γ-nitrogen. The corresponding diazo precursers can be obtained in high yields by treating β-keto esters **1** with TsN_3 in a basic medium (see the Supporting Information).

An initial survey of diazo esters **2** using $Rh_2(OAc)_4$ in dichloromethane gave trace amounts of the desired product, indicating the futility of a metal complex in the aromatic C–H insertion (Table 1, entry 1). Considering that two chelating bis-carboxylate ligand possesses more favourable kinetic stability in the C–H insertion reaction than the tetracarboxylate ligand,[11] we found that $Rh_2(esp)_2$ (α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid) could enhance the yield dramatically (Table 1, entry 2). The following screen of solvents and transition metal catalysts revealed that dichloromethane and $Rh_2(esp)_2$ were the best solvent and catalyst for this catalytic system (Table 1, entries 2–7). Further investigation of the N-protecting groups showed that the methanesulfonamide **2b** slightly decreased the reactivity, while the conversion was totally inhibited by acetamide **2c** even with increasing amount of catalyst (Table 1, entries 8 and 9). However, methylamine **2d** surprisingly delivered a predominant rearranged product **4d**, which was elucidated as an α,β-unsaturated ester through spectro-

scopic analysis (Table 1, entry 10). Several known transition metals that can promote the Wolff rearrangement, such as $Rh_2(OAc)_4$, Cu(I) and Ag(I), were incorporated with diazo precursor **2d** (Table 1, entries 10–14). Although Ag(I) is known to be more effective in facilitating the rearrangement than Cu(I) and Rh(II),[12] no improvement was observed until harsh conditions were employed. Treatment with silver oxide led to high reactivity and full conversion to the desired product, compared to the moderate yield with rhodium catalyst under the same conditions (Table 1, entry 15 and 16). Further screening supported that a less polar solvent was preferred in this reaction (Table 1, entries 17 and 18). It was also worthy of note that the self-thermal initiation without any catalyst can partially occur at high temperatures (Table 1, entry 19).

We tested the generality of the aromatic C–H insertion with different substituted anilines. For the electronically donating and neutral substrates, the reaction afforded the desired products with comparative yields and occurred exclusively at the *para*-position of the substituent groups, presumably avoiding steric hindrance (Scheme 2, **3a, 3e–l**). Similarly, the electron-withdrawing group, such as fluorine, was also tolerated in this reaction and gave a moderate yield (Scheme 2, **3k**). However, no quinoline or lactam product was observed under these conditions after changing the keto ester to a keto amide (Scheme 2, **3aa**), although it was previous reported by Afonso and co-workers that diazoacetamide could be converted to the lactam through intramolecular C–H insertion in their case.[4a]

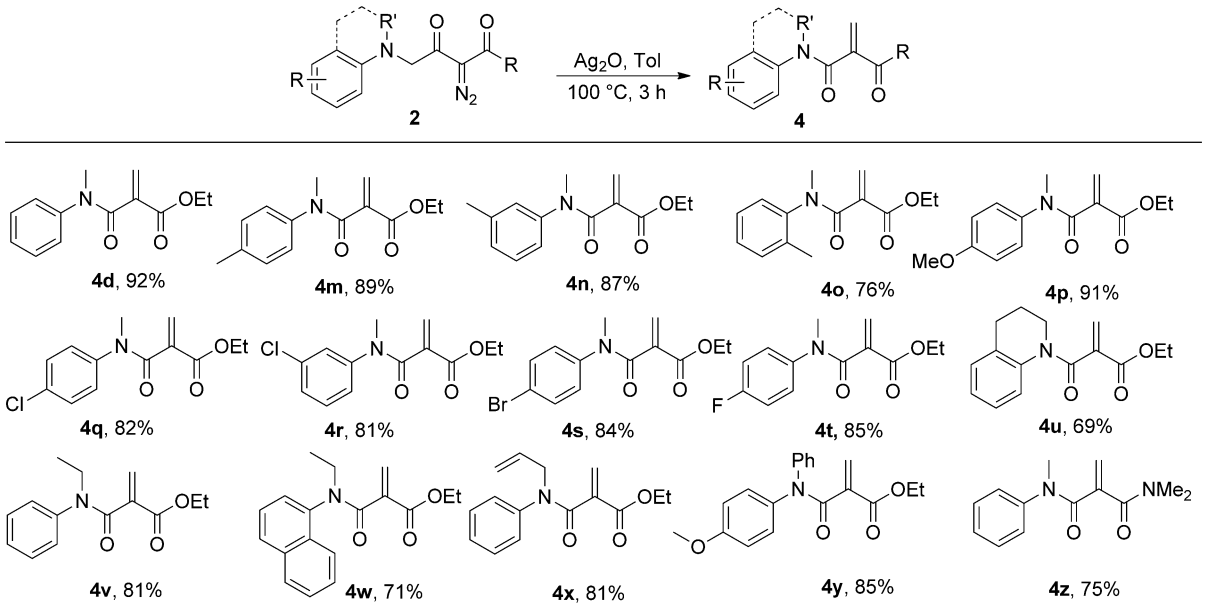


Scheme 2. Reaction scope of the aromatic C–H insertion reaction.

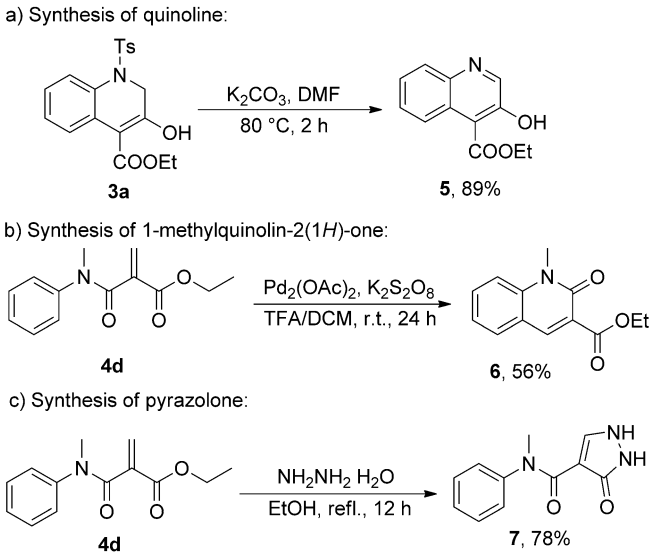
Regarding the rearrangement reaction, the exploration of the reaction scope revealed robust reliability. For a variety of electronic and regional substituents on the phenyl ring, the reaction afforded 2-carbamoylacrylates in high yields (Scheme 3). For example, it worked well with electron-neutral (Scheme 3, **4m–o**), electron-donating (Scheme 3, **4p**), and electron-withdrawing (Scheme 3, **4t**) substituents and good yields were observed with different regional substitutions including bulky *ortho*-substitution (Scheme 3, **4m**, **4n** and **4q**, **4r**). A set of alkyl substrates also delivered products with satisfactory yields, such as strained tetrahydroquinoline and bulky naphthalene (Scheme 3, **4u** and **4w**). The reaction also tolerated a double bond motif, providing the product instead of the formation of cyclopropanation (Scheme 3, **4x**). However, the dialkyamino-substituted substrate failed to give the rearranged product (data not shown), while the diarylamino-substituted precursor generated the carbamoylacrylate **4y** under either Ag_2O or $Rh_2(esp)_2$ catalysis [$Rh_2(esp)_2$ gave a 76% yield of **4y** and no C–H insertion product was observed]. In addition, the keto amide substrate can be successfully coordinated to the Wolff rearrangement as well (Scheme 3, **4z**).

Next, we concentrated on the synthetic versatility of dihydroquinoline and 2-carbamoylacrylate derivatives, especially to build heterocyclic scaffolds (Scheme 4). The dihydroquinoline **3a** underwent an elimination of *p*-toluenesulfonic acid to give quinoline **5**. Likewise, the 2-carbamoylacrylate also exhibited utility in several different reaction types, such as in the synthesis of 1-methylquinolin-2(1*H*)-one **6** and pyrazolone **7**, *via* C–H bond oxidative activation and hydrazinolysis, respectively. All the transformations proceeded in good yields under non-optimized conditions. Since these heterocyclic scaffolds are valuable in medicinal and agrochemical applications,[5,13] the α-diazo β-keto esters with different directing groups could serve as versatile and straightforward building blocks in the future studies.

A plausible mechanism is depicted in Figure 1. We propose that the first step is a metal insertion to form intermediate **A** *via* extrusion of N_2 for both processes. When the tosyl and mesyl groups are used as the directing groups, sulfonamides decrease the electron



Scheme 3. Reaction scope of the Wolff rearrangement.



Scheme 4. Synthetic transformations of **3a** and **4d**.

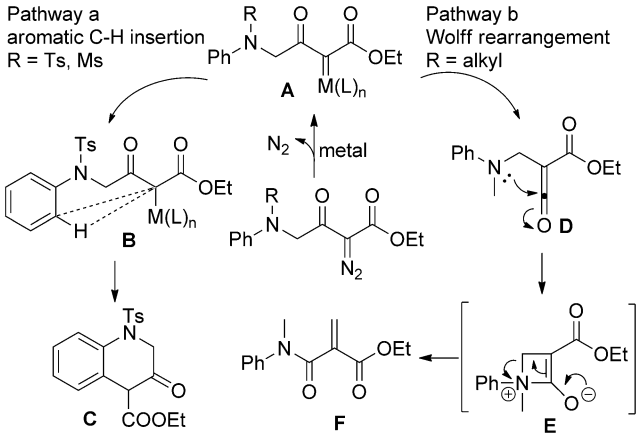


Figure 1. A plausible mechanism of the reactions.

density of the nearby methylene group so that C–H activation favored the more acidic C–H bond on the aromatic ring, which further generated aromatic insertion product **C**. Otherwise, in the case of aliphatic substituents as the directing groups, the enhanced electronic density of nitrogen allowed the neighbouring methylene group to participate in the formation of ketene intermediate **D** according to a concerted Wolff mechanism.[14] The nitrogen lone pair next attacked the ketene center to form azetidine enolate **E**. To this end, a stable carbamoylacrylate motif **F** was finally produced after subsequent electrocyclic ring opening.

In summary, we have found that the chemoselectivity in aromatic C–H insertion and rearrangement of α-diazo β-keto ester precursors is based on the different directing groups substantially. Sulfonamide substituents gave a C–H insertion product, while alkyl substituents underwent a rearrangement reaction. Considering the subsequent conversions to various heterocyclic structures under mild conditions, this protocol should be very useful for the rapid synthesis of bioactive analogues.

Experimental Section

Typical Procedure for the $Rh_2(esp)_2$-Catalyzed C–H Insertion Reaction of α-Diazo β-Keto Esters

A solution of α-diazo β-keto ester (0.2 mmol) in anhydrous CH_2Cl_2 (2 mL) was added *via* constant pressure funnel to a stirred solution of $Rh_2(esp)_2$ (0.5 mol%) in anhydrous CH_2Cl_2 (2 mL) at room temperature under a nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred for 6 h at room temperature until complete conversion was observed. The content was transferred directly onto silica and purified by eluting with petroleum ether/EtOAc (5:1). Removal of the solvent followed by drying under vacuum afforded **3** in high purity.

Typical Procedure for the Ag_2O-Catalyzed Rearrangement Reaction of α-Diazo β-Keto Esters

A solution of α-diazo β-keto ester (0.2 mmol) in Toluene (2 mL) was added Ag_2O (0.5 mol%) at room temperature under a nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred at 100 °C for 3 h until complete conversion was observed. Then, the solvent was cooled down to room temperature and concentrated under reduced pressure. The content was transferred directly onto silica and purified by eluting with petroleum ether/EtOAc (5:1). Removal of the solvent followed by drying under vacuum afforded **4** in high purity.

Acknowledgements

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References

[1] For selected reviews, see: a) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704; b) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; c) Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577; d) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417.

[2] For recent selected examples of the diazo compounds applied in aromatic C–H insertion, see: a) C. Tortoreto, T. Achard, W. Zeghida, M. Austeri, L. Guenee, J. Lacour, *Angew. Chem.* **2012**, *124*, 5949; *Angew. Chem. Int. Ed.* **2012**, *51*, 5847; b) W. Chan, S. Lo, Z. Zhou, W. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 13565; c) K. Takeda, T. Oohara, M. Anada, H. Nambu, S. Hashimoto, *Angew. Chem.* **2010**, *122*, 7133; *Angew. Chem. Int. Ed.* **2010**, *49*, 6979; d) M. B. Johansen, M. A. Kerr, *Org. Lett.* **2010**, *12*, 4956; e) G. Deng, B. Xu, J. Wang, *Tetrahedron* **2005**, *61*, 10811; f) L. Goldoni, G. Cravotto, A. Penoni, S. Tollari, G. Palmisano, *Synlett* **2005**, 927.

[3] For selected examples of the diazo compounds applied in rearrangements, see: a) N. Selander, B. T. Worrell, V. V. Fokin, *Angew. Chem.* **2012**, *124*, 13231; *Angew. Chem. Int. Ed.* **2012**, *51*, 13054; b) Y. Jiang, W. C. Chan, C. M. Park, *J. Am. Chem. Soc.* **2012**, *134*, 4104; c) M. Presset, Y. Coquerel, J. Rodriguez, *J. Org. Chem.* **2009**, *74*, 415; d) M. Vitale, T. Lecourt, C. G. Sheldon, V. K. Aggarwal, *J. Am. Chem. Soc.* **2006**, *128*, 2524; e) W. Shi, F. Xiao, J. Wang, *J. Org. Chem.* **2005**, *70*, 4318.

[4] a) L. F. R. Gomes, A. F. Trindade, N. R. Candeias, P. M. P. Gois, C. A. M. Afonso, *Tetrahedron Lett.* **2008**, *49*, 7372; b) H. Seki, G. I. Georg, *J. Am. Chem. Soc.* **2010**, *132*, 15512; c) N. R. Candeias, C. Carias, L. F. R. Gomes, V. Andre, M. T. Duarte, P. M. P. Gois, C. A. M. Afonso, *Adv. Synth. Catal.* **2012**, *354*, 2921; d) N. S. Y. Loy, A. Singh, X. Xu, C. M. Park, *Angew. Chem.* **2013**, *125*, 2268; *Angew. Chem. Int. Ed.* **2013**, *52*, 2212; e) S. Jansone-Popova, J. A. May, *J. Am. Chem. Soc.* **2012**, *134*, 17877.

[5] a) J. I. Seeman, *Angew. Chem.* **2007**, *119*, 1400; *Angew. Chem. Int. Ed.* **2007**, *46*, 1378; b) J. K. Baird, S. L. Hoffman, *Clin. Infect Dis.* **2004**, *39*, 1336; c) N. T. Abdel-Ghani, A. F. Youssef, M. A. Awady, *Farmaco* **2005**, *60*, 419; d) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. I. McPhail, G. A. Sim, *J. Am. Chem. Soc.* **1966**, *88*, 3888; e) R. Baumgartner, M. Walloschek, M. Kralik, A. Gotschlich, S. Tasler, J. Mies, J. Leban, *J. Med. Chem.* **2006**, *49*, 1239.

[6] W. Li, X. Liu, X. Hao, Y. Cai, L. Lin, X. Feng, *Angew. Chem.* **2012**, *124*, 8772; *Angew. Chem. Int. Ed.* **2012**, *51*, 8644.

[7] A. M. Jadhav, V. V. Pagar, R. S. Liu, *Angew. Chem.* **2012**, *124*, 11979; *Angew. Chem. Int. Ed.* **2012**, *51*, 11809.

[8] a) W. Chan, T. Kwong, W. Yu, *Org. Biomol. Chem.* **2012**, *10*, 3749; b) H. L. Wang, Z. Li, G. W. Wang, S. D. Yang, *Chem. Commun.* **2011**, *47*, 11336.

[9] For reviews, see: a) W. Kirmse, *Eur. J. Org. Chem.* **2002**, 2193; b) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091.

[10] a) M. Vitale, T. Lecourt, C. G. Sheldon, V. K. Aggarwal, *J. Am. Chem. Soc.* **2006**, *128*, 2524; b) X. Xu, Y. Qian, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 1244, and references cited therein.

[11] a) C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378; b) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2009**, *131*, 7558.

[12] R. R. Julian, J. A. May, B. M. Stoltz, J. L. Beauchamp, *J. Am. Chem. Soc.* **2003**, *125*, 4478.

[13] a) N. Uramaru, H. Shigematsu, A. Toda, R. Eyanagi, S. Kitamura, S. Ohta, *J. Med. Chem.* **2010**, *53*, 8727; b) D. Costa, A. P. Marques, R. L. Reis, J. L. F. C. Lima, E. Fernandes, *Free Rad. Bio. Med.* **2006**, *40*, 632.

[14] J. Fien, W. Kirmse, *Angew. Chem.* **1998**, *110*, 2352; *Angew. Chem. Int. Ed.* **1998**, *37*, 2232.

